

WHAT IS CLAIMED IS:

1. A method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of one of more of:

- 5 (a) an anti-angiogenic factor or anti-angiogenic agonist; and
(b) an inhibitor of angiogenic protein or pathway;

wherein said factor or agonist of (a) and said inhibitor of (b)

- (i) inhibits endothelial cell proliferation,
(ii) inhibits endothelial cell migration, and/or
10 (iii) induces endothelial cell apoptosis

thereby inhibiting said angiogenesis.

2. The method of claim 1 wherein the anti-angiogenic factor or agonist is TSP-1, angiostatin, interferon α , or interferon β .

3. The method of claim 1 wherein the anti-angiogenic factor or agonist is TSP-1 or a
15 anti-angiogenically functional derivative thereof.

4. The method of claim 1, wherein the angiogenic protein of (b) that is being inhibited is selected from the group consisting of HGF/SF, VEGF, FGF, PDGF, or IL-8

5. The method of claim 4, wherein the angiogenic protein being inhibited is VEGF.

6. The method of claim 1 wherein the inhibitor of (b) is a VEGF inhibitor that
20 inhibits VEGF expression or action, or expression or action of VEGF receptors.

7. The method of claim 6 wherein the inhibitor of is selected from the group consisting of an anti-VEGF antibody, an anti-VEGF receptor antibody, a decoy VEGF receptor, VEGF-Trap, a siRNA specific for VEGF, a siRNA specific for VEGF receptor, a peptidomimetic inhibitor of VEGF receptor activation.

8. The method of any of claims 1-7 wherein the inhibitor is the anti-VEGF mAb
25 termed Avastin®

9. The method of claim 1, wherein the inhibitor of (b) inhibits the HGF/SF-Met signaling pathway.

10. The method of claim 9, wherein the inhibitor is selected from the group consisting of (1) a neutralizing antibody specific for HGF/SF or Met, (2) an HGF/SF antagonist known as NK4, (3) a decoy Met receptor or fragment, (4) a genetically engineered polypeptides derivative of Met with inhibitory activity, (5) a Met-specific siRNA, (6) an inhibitor the kinase domain of Met, (7) an inhibitor that targets the multi-docking site of Met, and (8) another agent that decreases HGF/SF or Met expression.

11. The method of any of claims 1-7, 9 or 10 wherein said providing is to a subject *in vivo*, which subject is susceptible to, or at risk of, tumor growth or metastasis, or in which subject said tumor growth or metastasis is ongoing.

12. The method of claim 8 wherein said providing is to a subject *in vivo*, which subject is susceptible to, or at risk of, tumor growth or metastasis, or in which subject said tumor growth or metastasis is ongoing.

13. A method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of one of more inhibitors that target the MAPK pathway and inhibits upregulation of an angiogenic factor and/or inhibits down-regulation of an anti-angiogenic factor, thereby inhibiting said tumor angiogenesis.

14. The method of claim 13, wherein said one or more MAPK pathway inhibitors increase the expression or anti-angiogenic activity of TSP-1.

15. The method of claim 13 wherein said one or more MAPK pathway inhibitors decrease the expression or angiogenic activity of VEGF.

16. The method of any of claims 13-15, wherein the MAPK inhibitor is a MEK inhibitor.

17. The method of claim 16 wherein the MEK inhibitor is anthrax lethal factor or another MEK protease.

18. The method of claim 17 wherein the MEK inhibitor is anthrax lethal factor.

19. The method of claim 16 wherein the MEK inhibitor is a small organic molecule selected from the group consisting of PD98059, U0126 and PD184352.

20. The method of claim 1 which comprises providing effective amounts of (A) TSP-1 or a TSP-1 agonist or mimic in combination with (B) an anti-VEGF antibody or VEGF-Trap and/or (C) a MEK inhibitor.

21. The method of claim 20 which comprises providing effective amounts of (A) TSP-1, (B) an anti-VEGF antibody and/or (C) anthrax lethal factor.

22. A composition useful for inhibiting tumor angiogenesis comprising an effective amount or amounts of one of more of:

- (a) an anti-angiogenic factor or anti-angiogenic agonist; and
- (b) an inhibitor of angiogenic protein or pathway;

10 wherein said factor or agonist of (a) and said inhibitor of (b)

- (i) inhibits endothelial cell proliferation,
- (ii) inhibits endothelial cell migration, and/or
- (iii) induces endothelial cell apoptosis.

23. The composition of method of claim 22 wherein the anti-angiogenic factor or agonist is TSP-1, angiostatin, interferon α , or interferon β .

24. The composition of claim 22 wherein the anti-angiogenic factor or agonist is TSP-1 or a anti-angiogenically functional derivative thereof.

25. The composition of claim 22, wherein the angiogenic protein of (b) that is being inhibited is selected from the group consisting of HGF/SF, VEGF, FGF, PDGF, or IL-8

20 26. The composition of claim 25, wherein the angiogenic protein being inhibited is VEGF.

27. The composition of claim 22 wherein the inhibitor of (b) is a VEGF inhibitor inhibits VEGF expression or action, or expression of action of VEGF receptors.

25 28. The composition of claim 27 wherein the inhibitor of is selected from the group consisting of an anti-VEGF antibody, an anti-VEGF receptor antibody, a decoy VEGF receptor, VEGF-Trap, a siRNA specific for VEGF, a siRNA specific for VEGF receptor, a peptidomimetic inhibitor of VEGF receptor activation.

29.. The composition of any of claims 22-28 wherein the inhibitor is the anti-VEGF monoclonal antibody termed Avastin®.

30. The composition of claim 22, wherein the inhibitor of (b) inhibits the HGF/SF-Met signaling pathway.

5 31. The composition of claim 30, wherein the inhibitor is selected from the group consisting of (1) a neutralizing antibody specific for HGF/SF or Met, (2) an HGF/SF antagonist known as NK4, (3) a decoy Met receptor or fragment, (4) a genetically engineered polypeptides derivative of Met with inhibitory activity, (5) a Met-specific siRNA, (6) an inhibitor the kinase domain of Met, (7) an inhibitor that targets the multi-docking site of Met, and (8) another agent
10 that decreases HGF/SF or Met expression.

32. A pharmaceutical composition comprising the composition of any of claims 22-28, 30 or 31, and further comprising a pharmaceutically acceptable vehicle or excipient.

33. A pharmaceutical composition comprising the composition of claim 29 and further comprising a pharmaceutically acceptable vehicle or excipient.

15 34. A composition useful for inhibiting tumor angiogenesis comprising an effective amount or amounts of at least two inhibitors that target the MAPK pathway and inhibit upregulation of an angiogenic factor and/or inhibit down-regulation of an anti-angiogenic factor, and thereby inhibit said tumor angiogenesis.

20 35. The composition of claim 34, wherein said MAPK pathway inhibitors increase the expression or anti-angiogenic activity of TSP-1.

36. The composition of claim 34 wherein said MAPK pathway inhibitors decrease the expression or angiogenic activity of VEGF.

37. The composition of any of claims 34-36, wherein one of the MAPK pathway inhibitors a MEK inhibitor..

25 38. The composition of claim 37 wherein the MEK inhibitor is anthrax lethal factor.

39. The composition of any of claims 37 wherein the MEK inhibitor is a small organic molecule selected from the group consisting of PD98059, U0126 and PD184352.

40. A pharmaceutical composition comprising the composition of any of claims 34-36, and further comprising a pharmaceutically acceptable carrier or excipient.

41. A pharmaceutical composition comprising the composition of claims 37, and further comprising a pharmaceutically acceptable carrier or excipient.

5 42. A pharmaceutical composition comprising the composition of claims 38, and further comprising a pharmaceutically acceptable carrier or excipient.

43. A pharmaceutical composition comprising the composition of claims 39, and further comprising a pharmaceutically acceptable carrier or excipient.

10 44. The composition of claim 22 which comprises providing effective amounts of (A) TSP-1 or a TSP-1 agonist or mimic in combination with (B) an anti-VEGF antibody or VEGF-Trap and/or (C) a MEK inhibitor.

45. The composition of claim 44 which comprises providing effective amounts of (A) TSP-1, (B) an anti-VEGF antibody and/or (C) anthrax lethal factor.

15 46. A pharmaceutical composition comprising the composition of claim 44 or 45, and further comprising a pharmaceutically acceptable carrier or excipient.